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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,942	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45 and 48-65* is/are pending in the application.

4a) Of the above claim(s) *37,45,48-52 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36, 38-44, 53-57 and 59-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/05; 8/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed August 23, 2006 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 1-45, 48-65 and 69-80 were pending. Applicants canceled claims 69-80. No claims were added or amended. Therefore, claims 1-45 and 48-65 are currently pending. Claims 37, 45, 48-52, and 58 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 1-36, 38-44, 53-57, and 59-65 are examined on the merits. Please note that claim 58 remains withdrawn from consideration (e.g., see 8/23/06 Response, page 16, footnote). The inclusion of claim 58 with the rejoined claims expressed on page 2 of the 5/2/03 non-final office action was a typographical error. The correct status of the claims can be found on the PTOL-326 form and also on the last two lines of paragraph 1 of the 5/2/03 non-final office action stating, "1-36, 38-44, 53-57, 59-65, 69-79 are examined on the merits in this action" (i.e., claim 58 is not examined on the merits).

Withdrawn Objections/Rejections

4. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

5. Claims 1, 9-19, 21, 24-32, 38-41, 53-57, and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) in view of Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) (of record) as evidenced by International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3 and Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2.

For ***claim 1,*** Marasco et al. (see entire document) disclose a method of selecting polynucleotides which encode an intracellular immunoglobulin molecule, or fragment thereof, including a single-chain immunoglobulin whose expression induces a modified phenotype in a eukaryotic host cell (see Marasco et al., abstract; see also column 37, lines 37-60; see also column 9, lines 32-37; see also column 31 and 32 disclosing the synthesis and screening of mutant libraries of intracellular immunoglobulin fragments; see especially column 31, lines 48-52), which reads on the claimed invention. For example, Marasco et al. **(a)** disclose providing a population of host cells capable of expressing said intracellular immunoglobulin molecule, or fragment thereof, wherein individual host cells of said population can be induced to exhibit a predetermined modified phenotype, wherein said modified phenotype is induced to via binding of said intracellular

immunoglobulin molecule or fragment thereof to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity" starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, binds to the gp160 antigen in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious"; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160. Marasco et al. also disclose **(b-c)** introducing into said population of host cells a first/second library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of first intracellular immunoglobulin subunit polypeptides, each comprising a first immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region and wherein said second intracellular immunoglobulin subunit polypeptides combine with

said first intracellular immunoglobulin subunit polypeptides to form a plurality of intracellular immunoglobulin molecules (e.g., see paragraph bridging columns 11 and 12, "In one preferred embodiment, the genes encoding the light chain and heavy chain encode a linker to make a single chain antibody (sFv) ... The sFv typically comprises a single peptide with the sequence V_H-linker-V_L or V_L-linker-V_H [Please note that this is being interpreted as an antibody "fragment" e.g., see specification, page 26, paragraph 68, "The single-chain fragment may comprise a single polypeptide with the sequence V_H-linker-V_L or V_L-linker-V_H"]. The linker is chosen to permit the heavy chain and light chain to bind together in their proper conformational orientation"; see also column 30, Construction and Expression of Mutant Antibodies section starting at line 46, "Using any of these broadly neutralizing antibodies, mutant antibodies [i.e., a library] can be generated can be generated. One can use standard mutagenesis techniques to result in cDNA coding for different amino acids in the variable regions of the heavy chain such as the CDR3 region [i.e., a library of heavy chain variable regions]"; see also column 31, lines 44-50; see also column 21, paragraph 2, "gene for the antibody can encompass ... the heavy chain and light chain regions. In addition, the gene is operably linked to a promoter"). Marasco also disclose **(d)** permitting expression of said plurality of intracellular immunoglobulin molecules, or fragments thereof in said population of host cells under conditions wherein said modified phenotype can be detected" (e.g., see "Ability of Antibody To Envelope Glycoprotein To Inhibit Envelope Protein Biosynthesis And Activity" section starting on line 14 of column 35; see also column 23, lines 13-17; see also "Inhibition of Function By Intracellular Antibody" section starting

on column 4, line 9; see especially paragraph bridging columns 35 and 36, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited"). Thus, the expression of sFv105 intracellular antibodies results in a detectable change in phenotype with regard to the processing of gp160. Finally, Marasco also disclose **(c)** recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see column 31, lines 44-50, "Using the above-described technique, six mutant sFv105 antibodies were produced in which the amino acids in the CDR3 region of the heavy chain were replaced by random amino acids. One of the six mutants [recovered] designated R had a CDR3 region which coded for (SEQ ID NO:74)" see column 6, lines 29-34, "These antibodies can be produced and/or screened by standard techniques"; see also column 11, paragraph 2, "Thus, one can readily screen an antibody to insure that it has a sufficient binding affinity for the antigen"; see also column 12, lines 3-5, "then with phage display vectors pull out [i.e., recover] the antibodies with the different linkers and screen for the highest affinity single chain antibody generated"; see also column 13, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e., recover] antibodies of interest"; see also column 24, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e., recover] antibodies of interest").

For ***claim 9***, Marasco et al. disclose human antibodies (e.g., see column 21, line 36; see also column 22, line 11; see also column 27, line 45; see also column 28, paragraph 1).

For ***claims 10-17,*** Marasco et al. disclose both heavy and light constant/variable

regions (e.g., see column 21, paragraph 2, "gene for the antibody can encompass ... the heavy chain and light chain regions"; see also column 11, last two paragraphs; see also figures 1 and 2; see also column 30, paragraphs 1 and 2; see also column 31, last paragraph; see also column 33, paragraphs 1 and 2; see also column 11, line 31, which discloses "FAB" fragments, which contain both constant and variable regions; see also column 19, lines 11 and 12, "Once obtained, the V_H and V_L domains can be used to construct sFv, Fv or Fab fragments).

For ***claims 18, 19, 24--32, 38, 39***, Marasco et al. disclose the "eukaryotic" poxvirus vector (e.g., see column 26, lines 43-46, "Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used"; see also column 21, paragraph 3; see also column 25, last paragraph wherein RNA vectors are disclosed; see also column 18, lines 34 and 35 disclosing expression in the cytoplasm). Marasco et al. do not explicitly state that the vaccinia virus is a linear, double-stranded DNA vector. However, the Examiner contends that these would be inherent features of the virus as disclosed by the International Committee on Taxonomy of Viruses (e.g., see International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3, see especially page 2, Nucleic Acid section, "Virions contain one molecule of linear double stranded DNA"). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to

establish the difference. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, although Marasco et al. do not explicitly recite any of the poxvirus in claim genera in claim 32, the Examiner contends that these classification would be immediately envisioned as the poxvirus only contain only 11 different members (e.g., see Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2) in accordance with *In re Schauman*. When the reference teaches a small genus which places a claimed species in the possession of the public as in *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978), and the species would have been obvious even if the genus were not sufficiently small to justify a rejection under 35 U.S.C. § 102. See MPEP § § 2131.02 and 2144.08 for more information on anticipation and obviousness of species by a disclosure of a genus.

For ***claim 21***, Marasco et al. also disclose the use of a plasmid vector (e.g., see column 31, last paragraph; see also figure 3).

For ***claims 40 and 41***, Marasco et al. disclose various promoters including constitutive promoters (e.g., column 21, paragraphs 1 and 2).

For ***claims 53-57***, Marasco et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et a., page 9, second to last paragraph, "intracellular expression of an antibody to its target, for example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further

processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present"; see also page 8, paragraph 3, "Syncytium formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface"; see also paragraph bridging pages 37-39 and figures 9-12). Marasco et al. disclose an altered susceptibility to HIV infection (e.g., see column 23, paragraph 2).

For ***claims 59-62***, Marasco et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see column 16, last paragraph wherein localization sequences are disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teach localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, "Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal" section).

The prior art teachings of Marasco et al. differ from the claimed invention as follows:

For ***claim 1***, Marasco et al. fail to teach the introduction of a second library. Marasco only teaches the use of a first heavy chain variable library (e.g., see column 31, lines 44-47, "Using the above-described technique, six mutant sFv105 antibodies were produced in which the amino acids in the CDR 3 region of the heavy chain were replaced

by random amino acids").

However, Waterhouse et al. teach the following limitations that are deficient in Marasco et al.:

For ***claim 1***, Waterhouse et al. teach screening libraries of heavy/light chain antibodies that can be "co-selected" to produce antibodies (or fragments) with high affinity (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screen a library of intracellular antibodies as taught by Marasco et al. using two libraries (i.e., a library of heavy and light chains) as taught by Waterhouse et al. because Waterhouse et al. explicitly state that both the heavy and light chain regions can be varied simultaneously (e.g., see Waterhouse, column 1). Furthermore, a person of ordinary skill in the art would have been motivated to use two libraries to increase the affinity of the antibody. For example, Marasco et al. state, "mutants having different binding affinities to the envelope glycoprotein [can be] screened" (e.g., see Marasco et al., columns 31 and 32, Construction and Expression of Mutant Antibodies section; see especially, column 32, lines 40-52 wherein a library of six mutants were screened in COS cells), which demonstrates a need for high affinity antibodies. Furthermore, Waterhouse et al. state that such a need may be fulfilled by screening both the heavy and light chains (e.g., see Waterhouse et al., page 2265, paragraph 2 teaching the advantages of "co-selection" and the use of "large combinatorial" libraries; see also page 2265, column 1, paragraph 1; see also page 2266,

column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because both references use pairs of V_H and V_L antibody proteins. In addition, the structure/function relationship of antibodies and the molecular biology techniques needed to make said antibodies are well established (i.e., this is not an unpredictable art).

6. Claims 1-36, 38-44, 53-57, and 59-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) in view of Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266) (of record) and in further view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record) as evidenced by International Committee on Taxonomy of Viruses. ICTVdb Descriptions: 58. Poxviridae. Retrieved April 18, 2006, pages 1-3 and Wikipedia, the Free Encyclopedia. Poxviridae. Retrieved April 18, 2006, pages 1 and 2.

For ***claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62,*** Marasco et al. and Waterhouse et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71, 75-79.

For ***claim 23***, Marasco et al. teach the use of a plasmid vector (e.g., see column

31, last paragraph; see also figure 3).

The prior art teaching of Marasco et al. and Waterhouse et al. differ from the claimed invention as follows:

For ***claim 2-8, 10-20***, Marasco et al. and Waterhouse et al. fail to recite method steps for "biopanning" wherein the polynucleotides are recovered, introduced and expressed again in a population of host cells.

For ***claim 22***, Marasco et al. and Waterhouse et al. fail to disclose a multiplicity of infection (MOI) ranging from about 1 to about 10.

For ***claims 33-36***, Marasco et al. and Waterhouse et al. fail to disclose vaccinia. In addition, the references fail to disclose an attenuated vaccinia virus.

For ***claims 42-44***, Marasco et al. and Waterhouse et al. fail to disclose the T7 phage and p7.5 promoters.

For ***claims 63-65***, Marasco et al. and Waterhouse et al. fail to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in Marasco et al. and Waterhouse et al.:

For ***claim 2-8 and 10-20***, the combined references of Rowlands et al. and Zauderer et al. (see entire document) teach biopanning. For example, Zauderer et al. disclose steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity i.e.,

they use "biopanning" techniques (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure"). Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 22***, the combined references of Rowlands et al. and Zauderer et al. teach an MOI = 1 (e.g., see Zauderer et al., page 86, line 2).

For ***claims 33-36***, the combined references of Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia virus (e.g., see Rowlands, page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraph 3; see also page 4, paragraph 2; see also page 8, paragraph 1; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable

domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see also Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing "attenuated" viruses).

For ***claims 42-44***, the combined references of Zauderer et al. and Rowlands et al. disclose T7 phage promoters. For example, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see Rowlands page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter"; see also claim 6 wherein p7.5k, 11k and 19k are disclosed).

For ***claims 63-65***, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to select for a library of both heavy and light intracellular antibody chains as taught by the combined references of Marasco et al. and Waterhouse et al. using a vaccinia virus vector as taught by the combined references of Zauderer et al. and Rowlands et al. because the combined references of Marasco et al. and Waterhouse et al. explicitly state that any vector can be used including poxvirus (e.g., see Marasco et al.,

column 21, "However, the techniques described can readily be used to introduce the antibody genes into other cells, preferably human cells. For example, using a mammalian expression vector, such as ... pox vector ... These vectors can be used to transduce cells by standard techniques well known to the skilled artisan"; see also middle of column 26), which would include the vaccinia virus disclosed by the combined references of Zauderer et al. and Rowlands et al. (see above). Furthermore, one of ordinary skill in the art would have been motivated to make the vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells and Rowlands further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form."). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because the combined references of

Zauderer et al. and Rowlands et al. indicate that antibody libraries can be easily generated using a vaccinia virus. Furthermore, the combined references of Marasco et al. and Waterhouse indicate that the use of any vector is "routine" in the art (e.g., see Marasco et al., column 21, "These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan"). In addition, Rowlands et al. state, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]").

Response

7. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Not All Elements of the Claims Are Taught or Suggested by the Cited References ... The cited references do not teach or suggest a method of selecting polynucleotides which encode an intracellular immunoglobulin molecule or fragment thereof, whose expression induces a modified phenotype in a eukaryotic host cell upon binding to an

intracellular antigen ... Marasco refers broadly to therapeutic methods that involve the intracellular binding of an antibody to a target molecule so as to disrupt the normal activity of the target molecule ... The Examiner has cited to Marasco at columns 31 and 32 which, according to the Examiner, disclose 'the synthesis and screening of mutant libraries of intracellular immunoglobulin fragments.' (Office Action, page 4). The portion of Marasco cited by the Examiner refers to the construction and expression of mutant single chain antibodies (sFv) that specifically bind to the HN envelope glycoprotein gp120. (See Marasco, column 30, line 46, through column 3 1, line 52). The sFv of Marasco, referred to as "F105," is single molecule consisting of an antibody light chain linked to an antibody heavy chain via a linker. (See Marasco, Fig. 2). Marasco used PCR-based mutagenesis to create nucleic acid molecules that encoded variants of F105 containing mutations in the CDR3 of the heavy chain variable domain. (Marasco, column 31, lines 10-47). As noted by Marasco, 'mutants having different binding affinities to the envelope glycoprotein were screened.' (Marasco, column 31, lines 4 1-42). Thus, the purpose of the screening process mentioned in Marasco was not to select for polynucleotides which encode a first intracellular immunoglobulin subunit polypeptide that, when combined with a second intracellular immunoglobulin subunit polypeptide, form an intracellular immunoglobulin molecule that binds to an intracellular antigen and thereby induces a modified cellular phenotype. Instead, the screening of Marasco was conducted simply to identify sFv mutants with 'different binding affinities to the envelope glycoprotein.' Binding of the sFv mutants to the HIV glycoprotein would not induce a 'predetermined modified phenotype' in the cells. The screening mentioned in Marasco at columns 30-32 is therefore far outside the scope of the screening methods encompassed by the present claims." (e.g., see

8/23/06 Response, pages 17-21).

[1] In response to applicant's arguments against the Marasco reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicants have simply argued that Marasco does not teach all the claimed limitations and, in so doing, failed to acknowledge the other references as set forth in the 35 U.S.C. § 103(a) rejection above. For example, the Examiner has already admitted that Marasco et al. fail to teach the introduction of a second library (e.g., see 5/2/06 Rejection, page 10, paragraph 2 outlining the deficiencies of the Marasco et al. reference). That's why Marasco et al. is not being applied as 102 art.

In addition, contrary to Applicants' assertions, Marasco et al. disclose a modified phenotype (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity" starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFvl05 or sFvlO5-KDEL, binds to the gp160 antigen in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gpl20 and gp41 on their surface. Such particles are not considered as infectious"; see also column 35, last paragraph, "the COS sFvlO5-KDEL cells, processing of gp160 to gp120 is

partially inhibited . . .[wherein] sFvlO5-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17; see also see column 31, lines 44-50, "Using the above-described technique [i.e., screening], six mutant sFvlO5 antibodies were produced [i.e., a library] in which the amino acids in the CDR3 region of the heavy chain were replaced by random amino acids. One of the six mutants [recovered] designated R had a CDR3 region which coded for (SEQ ID NO:74)")). Furthermore, Applicants have broadly defined the term "modified phenotype" to encompass "a change in the form, character, or intensity of a physical or biochemical characteristic displayed by host cells under a particular set of environmental factors" (e.g., see specification, page 12, paragraph 39), which would encompass virtually any detectable physiological change.

[2] Applicants argue, "The Cited References Do Not Teach or Suggest Recovering Polynucleotides from Host Cells Which Exhibit a Modified Phenotype ... The Examiner, however, asserted that: Marasco also disclose (e) recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see column 31, lines 44-50, "Using the above described technique, six mutant sFvlO5 antibodies were produced in which the amino acids in the CDR3 region of the heavy chain were replaced by random amino acids. One of the six mutants [recovered] designated R had a CDR3 region which coded for (SEQ ID NO:74)"). (Office Action, page 6) ... The word "recovered" in brackets at page 6 of the Office Action was inserted by the Examiner and is not found in the portion of Marasco cited by the Examiner. In fact, Marasco does not mention recovering polynucleotides from cells at all ... Although Marasco mentions transfecting the mutated constructs into COS cells and screening for

mutants 'having different binding affinities to the envelope glycoprotein,' there is no indication that polynucleotides were recovered from the cells. Marasco refers to a particular mutant designated "R," and sets forth the amino acid sequence of the CDR3 of this antibody; however, there is no indication that the polynucleotide encoding " R was recovered from cells. The mutations in Marasco were made by site-directed PCR-based mutagenesis, meaning that the mutations were made before the clones were introduced into the COS cells. Accordingly, there would have been no reason for Marasco to have recovered the polynucleotides from the cells. Thus, contrary to the Examiner's implication, Marasco does not disclose or even suggest recovering the polynucleotide encoding "R" from cells." (e.g., see 8/23/06 Response, pages 21-22).

[2] The Examiner respectfully disagrees. The mutant libraries were produced using a "degenerative" NNS codon (e.g., see column 31, line 15). Thus, a person of skill in the art would not known which antibody binds to a particular target without isolating it and identifying its sequence. In addition, Applicants focus on the preferred embodiment set forth in column 31 is too narrow and unjustly limits the teaching of the reference. Marasco et al. explicitly state throughout the reference that "screening" is key to generating intracellular antibodies with high affinity (e.g., see column 6, lines 29-34, "These antibodies can be produced and/or screened by standard techniques"; see also column 11, paragraph 2, "Thus, one can readily screen an antibody to insure that it has a sufficient binding affinity for the antigen"; see also column 12, lines 3-5, "then with phage display vectors pull out [i.e., recover] the antibodies with the different linkers and screen for the highest affinity single chain antibody generated"; see also column 13, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e.,

recover] antibodies of interest"; see also column 24, lines 6 and 7, "One then screens the antibodies by standard techniques to find [i.e., recover] antibodies of interest"). Therefore, the "recovering the polynucleotides" would be immediately envisioned. Furthermore, even if, assuming arguendo, this recovery step is not taught by Marasco et al. alone, it would be taught in view of Waterhouse et al. as set forth in the rejection above (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1, "However larger 'primary' repertoires of phage antibodies should allow higher affinity fragments to be isolated [i.e., recovered]"). In addition, the Examiner notes that the "Zauderer/Rowlands" 103 rejection also teaches recovering polynucleotides including the use of "biopanning" techniques (e.g., see above Zauderer rejection, especially with respect to claims 2-8 and 10-20).

[3] Applicants argue, "the present claims specify that the polynucleotides of the first library are recovered from host cells "which exhibit said modified phenotype." In addition to the fact that Marasco does not teach or suggest recovering polynucleotides from cells at all, Marasco certainly does not teach or suggest recovering polynucleotides from host cells that exhibit a modified phenotype. In fact, Marasco admits that "[t]hese six mutants did not bind to the HIV-1 envelope protein." (Marasco, column 31, lines 5 1-52). If the six mutant anti-gpl20 antibodies of Marasco did not bind to the HIV-1 envelope protein, then there is absolutely no way that polynucleotides encoding these mutants could have been recovered from host cells that exhibited a modified phenotype. (It is noted that, in any event, the present claims specify that modified phenotype is induced via binding of the intracellular immunoglobulin molecule or fragment thereof to an intracellular antigen.)" (e.g., see 8/23/06 Response, page 23, paragraph 1).

[3] Again, the Examiner contends that Applicants' narrow focus on one preferred embodiment of Marasco et al. fails to appreciate the full teachings of the reference. For example, Marasco et al. state in the abstract, "The present invention relates to a method by which one can target an undesired target molecule or target antigen, preferably a protein. The method comprises the intracellular expression of an antibody ... [wherein said] antibody ... binds [intracellularly] to the target, thereby disrupting the target from its normal actions." Thus, modifying cellular phenotypes by "disrupting" a target from its normal action is clearly the main objective of this patent. Furthermore, the Marasco et al. talk at length about various phenotypes that can be altered including changing immune system recognition for organ transplants (e.g., see Marasco et al., column 7, lines 25 and 26), changing in intracellular processing and expression of proteins like gp160, gp120 and gp41 (e.g., see Marasco et al., column 7 and 8), altering signal transduction (e.g., see column 10, paragraph 1), etc. Limiting the teachings of Marasco et al. to one example wherein six peptides failed to bind the HIV-1 envelope protein simply isn't justified. Marasco et al. clearly teach methods for screening intracellular antibodies against a wide range of targets (in fact all intracellular targets) that would inherently and/or explicitly alter the phenotype and isolating those antibodies and/or their corresponding DNA to identify the antibody with the strongest affinity for the given target (e.g., see column 10, paragraph 2, see also paragraph bridging columns 11 and 12, "screen for the highest affinity single chain antibody generated [i.e., recover the ones that work]"). In addition, Applicants' arguments fail to appreciate the other references (e.g., Waterhouse, Zauderer, etc., see section [1] above).

[4] Applicants argue, "The Cited References Do Not Teach or Suggest Introducing a Second Library of Polynucleotides Into a Population of Eukaryotic Host Cells ... The method of

Waterhouse ... requires the infection of E. coli cells with phage particles. Since E. coli are not eukaryotic cells and since phage particles can only infect bacterial cells, it follows that Waterhouse does not teach or suggest introducing libraries of polynucleotides into eukaryotic host cells, as required by the present claims" (e.g., see 8/23/06 Response, pages 23 and 24).

[4] In response to applicant's argument that the phage particles must somehow be employed in eukaryotic cells, the Examiner notes that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the present case, the Examiner has never argued that the eukaryotic system should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. To the contrary, the Waterhouse et al. reference, when take as a whole, impliedly shows that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. That is, larger libraries produce higher affinity antibodies, which is a "numerical" advantage that is independent of the system (i.e., larger libraries in eukaryotic systems would produce higher affinity antibodies just like larger libraries in prokaryotic systems do). In addition, Applicants' arguments fail to appreciate the other references (e.g., Waterhouse, Zauderer, etc., see section [1] above).

[5] Applicants argue, "A Person of Ordinary Skill in the Art Would Not Have Been

Motivated to Modify or Combine the Cited References ..." (e.g., see 8/23/06 Response, bottom page 24).

[5] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, a person of ordinary skill in the art would have been motivated to use two libraries to increase the affinity of the antibody. For example, Marasco et al. state, "mutants having different binding affinities to the envelope glycoprotein [can be] screened" (e.g., see Marasco et al., columns 31 and 32, Construction and Expression of Mutant Antibodies section; see especially, column 32, lines 40-52 wherein a library of six mutants were screened in COS cells), which demonstrates a need for high affinity antibodies. Furthermore, Waterhouse et al. state that such a need may be fulfilled by screening both the heavy and light chains (e.g., see Waterhouse et al., page 2265, paragraph 2 teaching the advantages of "co-selection" and the use of "large combinatorial" libraries; see also page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). In addition, Applicants' arguments fail again to appreciate the other references (e.g., Waterhouse, Zauderer, etc., see section [1] above).

[6] Applicants argue, "the polynucleotides encoding the mutant single chain antibodies were not introduced into a eukaryotic host cell that could be induced to exhibit a predetermined modified phenotype via binding of the single chain antibodies to an intracellular antigen. Instead, the mutant polynucleotides of Marasco were introduced into COS cells. The single chain antibody of Marasco ("F105") is said to bind to an HIV-1 glycoprotein called gp120. There is no indication in Marasco that the COS cells, into which the mutant antibodyencoding polynucleotides were introduced, expressed the gp120 antigen. Even if the COS cells somehow did express the gp120 antigen, the binding of the single chain antibodies of Marasco to gp120 would not induce a 'predetermined modified phenotype,' as required by the present claims" (e.g., see 8/23/06 Response, page 25, first full paragraph).

[6] This repeated issue was adequately addressed in sections [1] and [3] above.

[7] Applicants argue, "Marasco does not teach or suggest introducing into a population of host cells a second library of polynucleotides encoding a plurality of second intracellular immunoglobulin subunit polypeptides. The Examiner has asserted that Waterhouse cures this deficiency, but as discussed above, Waterhouse deals specifically with the introduction of polynucleotides into bacteria and relies on the use of phage particles to infect bacterial cells. Thus, the method of Waterhouse is specific for bacteria and cannot be used in the context of eukaryotic cells (e.g., see 8/23/06 Response, pages 25 and 26).

[7] This repeated issue was adequately addressed in section [4] above.

[8] Applicants argue, "a person of ordinary skill in the art would have had absolutely no

motivation to modify the screening method of Marasco by introducing a second library of polynucleotides into the cells, as specified by the present claims. The F105 single chain antibody of Marasco contains both a heavy chain variable region and a light chain variable region. (See Marasco, Fig. 2). Thus, the F105 single chain antibody -- by itself-- is capable of binding to the gp120 antigen. Accordingly, a person of ordinary skill in the art would have had no reason to introduce even a single second polynucleotide encoding a second immunoglobulin subunit polypeptide into the cells used in Marasco, much less a library of polynucleotides encoding a plurality of intracellular immunoglobulin subunit polypeptides, as required by the present claims ... Indeed, the addition of an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region to a single chain antibody would not be expected to increase the affinity of the single chain antibody for its antigen" (e.g., see 8/23/06 Response, pages 25 and 26).

[8] Applicants have misinterpreted the Examiner's arguments. The Examiner has never set forth the proposition that "the addition of an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region to a single chain antibody would ... be expected to increase the affinity of the single chain antibody for its antigen" as purported. Consequently, Applicants' arguments are moot. To the contrary, the Examiner has repeatedly stated that "screening" larger libraries will produce antibodies with higher affinities. Therefore, the use of "two" libraries as opposed to "one" library will lead to greater diversity and thus higher affinities. Any interpretation to the contrary is simply not justified. Furthermore, a person of skill in the art would have been motivated to combine the references for the reasons stated in the rejection and as noted again in section [5] above.

[9] Applicants argue, "neither Waterhouse nor Marasco suggest a way by which one could adapt the system of Waterhouse so it could be used in eukaryotic host cells" (e.g., see 8/23/06 Response, paragraph bridging pages 26 and 27).

[9] This argument is inconsistent with 35 U.S.C. § 103(a) statute itself. Any "primary" reference that fails to teach a particular limitation in a multi-reference 35 U.S.C. § 103(a) rejection will necessarily, as a matter of law, also fail to teach how to how to "adapt" that system for the missing limitation. If this were not the case, then the secondary reference would not be required. Thus, Applicants' *per se* rule requiring an "adaptation" of this missing element be shown in the primary reference itself is untenable. In addition, obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." In re O'Farrell, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, a person of ordinary skill in the art would reasonably have expected to be successful because both references use pairs of V_H and V_L antibody proteins. In addition, the structure/function relationship of antibodies and the molecular biology techniques needed to make said antibodies are well established (i.e., this is not an unpredictable art). In addition, Applicants' arguments fail again to appreciate the other references (e.g., Waterhouse, Zauderer, etc., see section [1] above).

[10] Applicants argue, "Since the system of Waterhouse is technologically specific for bacterial cells, a person of ordinary skill in the art would have had no motivation to combine the system of Waterhouse with the screen set forth in Marasco" (e.g., see 8/23/06 Response, page 27, paragraph 1).

[10] This statement is not even consistent with Applicants' own specification, which clearly admits that a person of skill in the art would look to phage display. For example, Applicants state, "Usually, candidate antibodies for use as intrabodies are initially identified in the phage display screening" (e.g., see specification, page 2, paragraph 5). Thus, Applicants admit that a person of skill in the art would "routinely" look toward phage display for solutions in finding high affinity intrabodies. Thus, Applicants' implicit argument that these two systems do not represent analogous art is without merit. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see *In re Paulsen* 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem).

Applicants also admit, "a screening method for predicting which single-chain Fv fragments (scFv) will function as intrabodies in mammalian cells was developed" (e.g., see specification, page 3, paragraph 3), which clearly links the "mammalian" cells to the "bacterial" scFv phage display in direct contrast to all of Applicants' statements above. Furthermore, to the extent Applicants are implicitly trying to argue again that, using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host, the Examiner again notes that that the Waterhouse et al. reference is not being relied upon for this purpose. The Examiner has never made such a contention and it is not at issue in this case. Waterhouse is being relied upon for the reasons set forth in the rejection, much the same way that Applicants' relied on "phage display" references

in their specification. Again, the Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Waterhouse et al. reference, when take as a whole, impliedly shows that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. In addition, Applicants' arguments fail again to appreciate the other references (e.g., Waterhouse, Zauderer, etc., see section [1] above).

[11] Applicants argue, "As explained in detail in Section I.A., above, the rejection ... based on Marasco and Waterhouse is in error because not all elements of the claims are taught or suggested by these references, and a person of ordinary skill in the art would not have been motivated to modify or combine the references. Neither Rowlands nor Zauderer cure the deficiencies of Marasco and Waterhouse, and neither reference provides a motivation to modify or combine the cited references to arrive at a method that falls within the scope of the currently presented claims" (e.g., see 8/23/06 Response, page 28, paragraph 1).

[11] To the extent that Applicants are merely repeating their previous arguments (e.g., in Section I.A.), the Examiner contends that those issues were adequately addressed in sections [1]-[10] above. To the extent that Applicants are further stating that there is no motivation to combined the Rowland and/or Zauderer et al. references to arrive at the presently claimed methods, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells and Rowlands further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.").

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

8. Claims 1-36, 38-44, 53-57, and 59-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-122

of U.S. Patent Application Serial No. 09/987,456 (referred to herein as '456) (especially claims 84, 88-92, 96, 97, 99, 103, 107-122) in view of Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) and Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) (of record) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For ***claim 1***, the '456 application claims discloses a method of selecting polynucleotides which encode an immunoglobulin molecule, or fragment thereof (e.g., see claim 84). In addition, the '456 application discloses providing a population of eukaryotic host cells capable of expressing said immunoglobulin molecule (e.g., see claim 84, step (a)). The '456 application also disclose introducing into said population of host cells a first and second library of polynucleotides, through operable association with a transcriptional control region, a plurality of first intracellular immunoglobulin subunit polypeptides, each comprising a first immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain region (e.g., see claim 84, steps (a)(ii) and (b)(ii)). The '456 application also disclose combining said second intracellular immunoglobulin subunit polypeptide with said fist subunit to form a plurality of immunoglobulin molecules (e.g., see claim 84, step (b)). The'456 application

also discloses permitting expression of said plurality of immunoglobulins and recovering the polynucleotides of said first library (e.g., see claim 84, step (e)).

For ***claims 2-8 and 10-20***, the '456 application also discloses recovering the polynucleotides and permitting them to be expressed multiple times for the purpose of increasing ligands with higher affinity i.e., biopanning (e.g., see claims 88-92).

For ***claim 9***, the '456 application discloses human antibodies (e.g., see claims 84, 93, 94, 127, 128 and 131).

For ***claims 10-17,*** the '456 application discloses both heavy and light constant/variable regions (e.g., see claims 84, 96, 97, 107, 110, 113, 116, 117 and 120).

For ***claims 18, 19, 24-35, 38, 39***, the '456 application discloses the eukaryotic poxvirus vector including vaccinia (e.g., see claims 84, 88, 89, 90, 92, 107, 108, 109, 110, 111, 112, 114, 115, 118 and 119).

For ***claim 22***, the '456 application discloses a multiplicity of infection (MOI) ranging from about 1 to about 10 (e.g., see claim 99)

The '456 application differs from the claimed invention as follows:

For ***claim 1***, the '456 application fails to disclose selecting an "intracellular" immunoglobulin whose expression induces a modified phenotype in a eukaryotic cell and permitting expression of said plurality of intracellular immunoglobulins under condition wherein said modified phenotype can be detected.

For ***claims 21 and 23***, the '456 application fails to disclose the use of a plasmid vector.

For ***claims 36***, the '456 application fails to disclose an attenuated form of

vaccinia.

For ***claims 40 and 41***, the '456 application fails to disclose various promoters including constitutive promoters.

For ***claims 42-44***, the '456 application fails to disclose the T7 phage and p7.5 promoters.

For ***claims 53-57***, the '456 application fails to disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen.

For ***claims 59-62***, the '456 application fails to disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence.

For ***claims 63-65***, the '456 application fails to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Marasco et al., Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in '456:

For ***claim 1***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. (see entire documents) teach the intracellular antibodies and their use to induce a phenotypic change by binding to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to

Inhibit Envelope Protein Biosynthesis And Activity starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, to in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious.; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.").

For ***claims 21 and 23***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. also disclose the use of a plasmid vector (e.g., see Marasco et al. column 31, last paragraph; see also figure 3).

For ***claims 33-36***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia virus (e.g., see Rowlands, page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraph 3; see also page 4, paragraph 2; see also page 8, paragraph 1; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see also Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing "attenuated" viruses).

For ***claims 40 and 41***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose various promoters including constitutive promoters (e.g., Marasco et al., column 21, paragraphs 1 and 2).

For ***claims 42-44***, the combined references of Marasco et al., Zauderer et al. and Rowlands et al. disclose the p7.5 and T7 phage promoters (e.g., see Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter"; see also claim 6 wherein p7.5k, 11k and 19k are disclosed).

For ***claims 53-57***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-consitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et a., column 9, second to last paragraph, "intracellular expression of an antibody to its target, for example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present"; see also column 8, paragraph 3, "Syncytium formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface"; see also columns 37-39 and figures 9-12).

For ***claims 59-62***, the combined references of Marasco et al., Rowlands et al. and

Zauderer et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see Marasco, column 16, last paragraph wherein localization sequences are disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teach localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, "Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal" section).

For ***claims 63-65***, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies disclosed by the '456 application using intracellularly expressed and/or localized antibodies as taught by the combined references of Marasco et al., Rowlands et al. and Zauderer et al. because Marasco et al., for example, explicitly state that pox virus can be used to express intracellular antibodies (e.g., see Marasco column 26, lines 43-46, "Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used"), which would encompass the vaccinia virus disclosed by the '456 application. Furthermore, Rowlands et al. further indicate that this vector can be used to create fully

functional antibodies that can still undergo glycosylation which is advantageous for mammalian processing (e.g., see Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin."). Finally, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. teach that antibodies can easily be expressed in vaccinia virus (e.g., see Rowlands et al., page 4, paragraph 3, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form."). Furthermore, Marasco et al. indicate that the use of any vector is "routine" in the art (e.g., see Marasco et al., column 21, "These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan"). In addition, Rowlands et al. state, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 1-36, 38-44, 53-57, and 59-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application Serial No. 10/465,808 (referred to herein as '808) in view of Marasco et al. (U.S. Patent No. 5,851,829) (Date of Patent is **December 22, 1998**) and Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) (of record) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) (of record). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For ***claim 1, 10-17,*** the '808 application discloses a method for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule (e.g., see '808, claim 46). The '808 application also discloses introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity (e.g., see claim 46, step (a); see also claim 80 disclosing the use of mammalian host cells which would inherently be permissive for vaccinia virus infectivity). The '808 application also discloses a first library of polynucleotides encoding through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides (e.g., see '808 application, claim 46, step (a); see also claims 59 and 68 disclosing constant heavy chain region; see also claims 128). In addition, the '808 application discloses each first

immunoglobulin subunit polypeptide comprising a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region (e.g., see '808, claim 46 claim 128, step (a)(i); see also claims 59, 60, 61, 62, 63, 66, 67, 68, 70 and 98 disclosing use of "heavy" chains). The '808 application also discloses an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region wherein said variable region corresponds to said first constant region (e.g., see '808, claim 46(a)(ii); see also claims 69, 70, 71 and 99 disclosing the use of "light" chains). The '808 application also discloses introducing into said host cells a second library of polynucleotides encoding through operable association with a transcriptional control region a plurality of second immunoglobulin subunit polypeptides each comprising (e.g., see '808, claim 46(b); see also claim 80). In addition, the '808 application discloses a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region or a light chain constant region wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region (e.g., see '808, claim 46(b)(i)). The '808 application also discloses an immunoglobulin variable region selected from the group consisting of heavy chain variable region ad a light chain variable region, wherein said variable region corresponds to said second constant region (e.g., see '808, claim 46(b)(ii). The '808 also discloses said second immunoglobulin subunit polypeptide that is capable of combining with said first immunoglobulin polypeptide to form an immunoglobulin molecule (e.g., see claim 46(b)(iii)). Finally, the '808 application teaches permitting expression of immunoglobulin molecules, contacting said

immunoglobulin molecules with an antigen, and recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see claim 46, steps (c)-(e)).

For ***claims 2-8 and 20,*** the '808 application disclose repetitive steps for "biopanning" a library (e.g., see '808, 48, 52, 115 and 123).

For ***claim 9***, the '808 application discloses human antibodies (e.g., see claim 58).

For ***claims 18, 19, 20, 24--35, 38, 39***, the '808 application discloses the eukaryotic poxvirus (e.g., see claims 85-88, 94 and 95).

For ***claim 22***, the '808 application discloses a multiplicity of infection (MOI) ranging from about 1 to about 10 (e.g., see claim 76).

For ***claims 40-44***, the '808 application discloses various promoters including T7 phage and p7.5 (e.g., see claims 92-96).

The '808 differs from the claimed invention as follows:

For ***claim 1***, the '808 application fails to disclose selecting an "intracellular" immunoglobulin whose expression induces a modified phenotype in a eukaryotic cell and permitting expression of said plurality of intracellular immunoglobulins under condition wherein said modified phenotype can be detected. The '808 application also fails to disclose the single chain embodiment described, for example, in claim 69.

For ***claims 21 and 23***, the '808 application fails to disclose the use of a plasmid vector.

For ***claims 36***, the '808 application fails to disclose an attenuated form of vaccinia.

For ***claims 53-57***, the '808 application fails to disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen.

For ***claims 59-62***, the '808 application fails to disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence.

For ***claims 63-65***, the '808 application fails to disclose epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

However, Waterhouse, Rowlands et al., and Zauderer et al. teach the following limitations that are deficient in Marasco et al.:

For ***claim 1***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. (see entire documents) teach the use of intracellular antibodies including the induction of a phenotypic change by binding to an intracellular antigen (e.g., see figure 3; see also columns 35 and 36, section entitled "Ability of Antibody Envelope Glycoprotein to Inhibit Envelope Protein Biosynthesis And Activity starting on line 16 of column 34 disclosing a modified phenotype, decreased envelope protein biosynthesis, that occurs when the intracellular antibody, sFv105 or sFv105-KDEL, to in COS cells; see also column 8, paragraph 1, "the method of using intracellular antibodies to bind to the newly synthesized gp160 in the lumen of the endoplasmic reticulum and inhibit its

transport to the Golgi apparatus, greatly reduces the amount of protein available for cleavage to gp120 and gp41. Accordingly, the viral particles produced have greatly diminished amounts of gp120 and gp41 on their surface. Such particles are not considered as infectious.; see also column 35, last paragraph, "In the COS sFv105-KDEL cells, processing of gp160 to gp120 is partially inhibited ... [wherein] sFv105-KDEL specific binding to the HIV-1 glycoprotein"; see also column 34, "Ability of Antibodies to be Expressed in Mammalian Cells" section; see also column 23, lines 13-17). Thus, the intracellular antibody, sFv105, induces a modified phenotype, change in gp120 biosynthesis and particle infectivity, by binding to an intracellular antigen, gp160; see also Rowlands et al., page 4, paragraphs 2 and 3, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin. It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form.").

For ***claims 21 and 23***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. also disclose the use of a plasmid vector (e.g., see Marasco et al. column 31, last paragraph; see also figure 3).

For ***claims 33-36***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. teach the use of vaccinia virus including an attenuated form of vaccinia

virus (e.g., see Rowlands, page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraph 3; see also page 4, paragraph 2; see also page 8, paragraph 1; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see also Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., page 34, last two paragraphs disclosing "attenuated" viruses).

For ***claims 53-57***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose host cells that comprise a cell surface antigen that is operably associated with constitutive/non-constitutive promoters and wherein said modified phenotype is expression of said cell surface antigen (e.g., see Marasco et a., page 9, second to last paragraph, "intracellular expression of an antibody to its target, for

example, the antibody to the [HIV] envelope glycoprotein ... results in an antibody that binds the target, e.g. envelope glycoprotein ... and prevents further processing ... One could even have the antibody under the control of a promoter that will be specifically activated by the target (e.g. an HIV LTR) thereby only turning the antibody on when the target is present"; see also page 8, paragraph 3, "Syncytium formation is mediated solely by the HIV-1 envelope protein expressed on the infected cell surface"; see also paragraph bridging pages 37-39 and figures 9-12). The '808 application discloses an altered susceptibility to HIV infection (e.g., see column 23, paragraph 2).

For ***claims 59-62***, the combined references of Marasco et al., Rowlands et al. and Zauderer et al. disclose heterologous polynucleotides within the library wherein said heterologous polynucleotide is common to each member of the library or its fusion to the first intracellular immunoglobulin subunit polypeptides such as a targeting sequence (e.g., see Marasco, column 16, last paragraph wherein localization sequences are disclosed; see also column 33, line 40; see also column 13, line 40 wherein KDEL is disclosed). Furthermore, Marasco teach localization in the endoplasmic reticulum using a KDEL-tagged sFv intrabody (e.g., see Marasco, column 13, middle paragraph; see also column 20, paragraph 2; see also column 22, second to last paragraph; see also column 29, "Construction and Eukaryotic Expression of F105 Single Chain Antibodies With and Without SEKDEL Endoplasmic Retention Signal" section).

For ***claims 63-65***, Zauderer et al. disclose the use of epitope tags such as 6-Histidine tags for purification of fusion proteins (e.g., see Zauderer et al., page 33, middle paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies disclosed by the '808 application using intracellularly expressed and/or localized antibodies as taught by the combined references of Marasco et al., Rowlands et al. and Zauderer et al. because Marasco et al., for example, explicitly state that pox virus can be used to express intracellular antibodies (e.g., see Marasco column 26, lines 43-46, "Other mammalian expression vectors such as herpes virus expression vectors, or pox virus expression vectors can also be used"), which would encompass the vaccinia virus disclosed by the '808 application (e.g., see '808 application, claims 85-88). Furthermore, Rowlands et al. further indicate that this vector can be used to create fully functional antibodies that can still undergo glycosylation which is advantageous for mammalian processing (e.g., see Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin."), which is a preferred embodiment of the '808 application (e.g., see '808 application, claims 58 and 80). Finally, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. teach that antibodies can easily be expressed in vaccinia virus (e.g., see Rowlands et al., page 4, paragraph 3, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form."). Furthermore, Marasco et al.

indicate that the use of any vector is "routine" in the art (e.g., see Marasco et al., column 21, "These vectors [pox virus] can be used to transduce cells by standard techniques well known to the skilled artisan"). In addition, Rowlands et al. state, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade. Over 75 different virus gene products and a variety of other proteins including growth factors, cell surface antigens, oncogenes, bacterial structural proteins and enzymes, and protozoan proteins have been expressed in vaccinia for a variety of purposes [i.e., this is not an unpredictable art]").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

10. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Applicants respectfully request that this rejection be held in abeyance until the remaining issues outstanding in this application have been resolved" and cite MPEP 804.I.A.1 in support of this position (e.g., see 8/23/06 Response, page 29).

The provisional rejections will not be held in abeyance. A provisional double patenting rejection is NOT the only rejection remaining in the present application and, as a result, the

double patenting rejection is proper.

Accordingly, the double patenting rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
November 3, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER